REMARKS

Claims 1-13 are pending in this application. Applicants appreciate the withdrawal of certain claim rejections. Reconsideration of the remaining rejections is respectfully requested for the reasons that follow.

Amendments

Claim 1 is amended to clarify that the dimers and/or multimers present in the mixture and being separated from the polypeptide monomers are dimers and/or multimers of such polypeptide monomers. Thus, the claims explicitly require that the mixture contain this particular type of polypeptide dimer and/or multimer and clarify and identify specifically the dimers and/or multimers from which the monomer is separated. Support can be found at least on page 2, line 25 and page 14, line 23.

Rejections under 35 USC §102

Claims 1-2, 5-7, and 9-13 are rejected under 35 USC §102(b) as being anticipated by Yang *et al.*, Journal of Chromatography, A 743 (1996). The Examiner asserts that Yang *et al.* teaches applying a mixture (which includes IgG's, ascites and sera) to a cation-exchange chromatography resin with pH's in the 6-7 range or to an anion-exchange resin with pH's in the 6-9 range and thus does teach separation of monomers from a mixture of dimers and multimers (serum and ascites).

Since claim 1 is now clearly directed to separating polypeptide monomers from their own dimers and/or multimers present in the mixture, Yang *et al.* is not applicable. Yang *et al.* is separating polypeptide monomers from other monomeric forms thereof (such as differently glycosylated or post-translationally different IgGs), or from totally different polypeptide monomers contained in the ascites and sera. However, Yang *et al.* contains no explicit or inherent disclosure of separation of such monomers from their own dimers and/or multimers. All the figures are consistent with these observations. The Examiner has not provided or pointed to any evidence or passages in Yang *et al.* to refute applicants' assertions that Yang *et al.* is not separating polypeptide monomers from dimers and/or multimers of such polypeptide monomers as now claimed, as distinguished from separating them from other dimers and/or multimers that may be naturally contained in ascites and sera. Indeed, Yang *et al.* provides no evidence that dimers and multimers of the

polypeptides disclosed therein are even contained in the ascites and sera from which they are purified. Since none of the data or disclosure of Yang *et al.* relates to the presently claimed aspect, Yang *et al.* cannot anticipate the instant amended claims.

In view of the absence of explicit or implicit disclosure in Yang *et al.* of a separation of monomers from their own dimers and/or multimers, and since claims 2-13 depend on amended claim 1, applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-2, 5-7, and 9-13 under 35 USC §102(b) over Yang *et al.*

Claims 1, 2, 5, and 8-13 are rejected under 35 USC §102(b), which should, in fact, be §102(a),[1] as being anticipated by Hahn *et al.*, Chromatography, 795, 277-287 (1998).

The Examiner urges that Hahn *et al.* teaches elution of the IgG monomers from a mixture (bovine whey) which contains monomers and dimers or multimers, and thus is directly applicable to the present claims. According to the Office, applicants have provided no evidence to support their assertion that the mixture taught in Hahn *et al.* does not contain dimers and/or multimers.

While the bovine whey may well contain dimers and multimers, Hahn *et al.* provides no explicit or implicit disclosure that the polypeptide monomer being purified from the bovine whey is separated from its own dimers and/or multimers, as required by the instant claims. There is further no evidence that such dimers and/or multimers are even present in the bovine whey. In point of fact, Hahn *et al.* teaches separation of various different proteins from each other, all of which are contained in bovine whey, such as IgG from lactoferrin and from lactoperoxidase (see, e.g., Table 1 on page 280). As with Yang *et al.*, there is no evidence in Hahn *et al.* that any separation has occurred between the monomer and any of its own dimers or multimers present in the mixture, as required by the instant claims, as opposed to dimers and/or multimers that may naturally be present in bovine whey.

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[1] In the previous Office Action mailed December 8, 1999, the Examiner indicated that the rejection over Hahn *et al.* was under 35 USC §102(a) (see page 3, paragraph 5 of Paper No. 4). This is properly a §102(a) reference because it was published Feb. 6, 1998 and the provisional application upon which the instant application claims priority was filed June 1, 1998, less than one year thereafter.

Because there is no anticipation by Hahn *et al.* of claim 1, and all other rejected claims depend on claim 1, applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 USC §102(a) over this reference.

Rejections under 35 USC §103

Claims 1-2 and 4-13 are rejected under 35 USC §103(a) as being unpatentable over Yang *et al.* in view of US 4,764,279 (Tayot *et al.*).

Yang *et al.* is discussed above as lacking a disclosure or suggestion of separation of a polypeptide monomer from dimers and/or multimers of such monomer as now instantly claimed, but rather describing monomer/monomer separation or separation of two different and unrelated proteins contained in a mixture. Tayot *et al.* fails to compensate for the deficiencies in Yang *et al.* because the blood mixture, while inherently containing dimers and multimers as stated by the Examiner, does not necessarily contain the mixture of dimers and/or multimers of the polypeptide monomer as now claimed, and even if it did, Tayot *et al.* does not disclose or suggest how one skilled in the art might separate proteins from their own dimers or multimers. Instead, hemoglobin, gamma-globulins, and albumin are separated from each other and presumably also from other unrelated proteins in the blood (see, e.g., claim 1), or hemoglobin and albumin are separated from each other and presumably also from other unrelated proteins in the blood (see, e.g., claim 10). These protein moieties are not related as monomers and dimers of such monomers and/or multimers of such monomers, as is required in the instantly claimed method.

Further, this combination of references would not have disclosed or suggested the unexpectedly high minimum purity and yield levels claimed by applicants, e.g., greater than 99.5% and greater than 90%, respectively.

Since claim 1 is patentable over the combination of references as discussed above, and all rejected claims are dependent thereon, reconsideration and withdrawal of the rejection of the claims under 35 USC §103 over Yang *et al.* in view of Tayot *et al.* is respectfully requested.

Claims 1-3 and 5-13 are rejected under 35 USC §103(a) as being unpatentable over Yang *et al.* and Hahn *et al.* in view of the Oncogene Science catalog 1992, pages 18 and 35.

The irrelevance of Yang *et al.* and Hahn *et al.* is noted above. The Oncogene Science publication merely mentions research-grade antibodies that are offered for sale and their potential applications. The Examiner states that this reference is cited to set forth the desirability of purification of the specific antibodies of claim 3. However, page 34 of the Oncogene Science reference, in the footnote at the bottom of the table on Ordering Information, states that "All antibodies (1.0 ml) are highly purified to prevent degradation." Hence, under the test of *In re Keller*, 288 USPQ 871 (CCPA 1981) cited by the Examiner, what the combined teachings of the references cited herein would have suggested to one of ordinary skill in the art is that the antibodies in the then-current state of the art were already highly purified and did not require further purification, and that, even if they needed further purification, they could be separated from other monomeric forms thereof or from other monomeric proteins that are different. The combined references would not have suggested the claimed invention as set forth above, particularly with the purity and yield results. There is nothing in the collection of references that would have motivated the skilled artisan to purify the polypeptide monomers from their dimers and multimers using the claimed method at the priority date.

Hence, reconsideration and withdrawal of the rejection of claims 1-3 and 5-13 under 35 USC §103(a) as being unpatentable over Yang *et al.* and Hahn *et al.* in view of the catalog is respectfully requested.

Information Disclosure Statement

On July 26, 2000 applicants mailed to the USPTO a Second Supplemental Information Disclosure Statement citing three more references (16-18). Applicants have noticed that the PTO-1449 form accompanying this Statement was not returned initialed by the Examiner with the latest Office Action. Therefore, another copy of this Second Supplemental Information Disclosure Statement is enclosed for the Examiner's convenience. Applicants request that the Examiner initial and sign the form attached, if not already done with the original, and return it to the applicants in due course for their records. If the Examiner needs copies of the cited references, she is encouraged to call the undersigned attorney to arrange to have them sent to the USPTO.

It is believed that all the currently presented claims are in condition for allowance, and a notice to that effect is earnestly solicited. If the Examiner has any questions, she should feel free to call the undersigned attorney at the number indicated below.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

GENENTECH, INC.

Date: March 5, 2001

By: Janet E. Hasak

Janet E. Hasak
Reg. No. 28,616
Telephone: (650) 225-1896

Enclosure: Second Supplemental Information Disclosure Statement mailed July 26, 2000.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claim 1 as follows:

1. (Amended) A method for separating [a] polypeptide monomers from a mixture comprising said polypeptide monomers, and dimers or multimers of said polypeptide monomers or both dimers and multimers of said polypeptide monomers, wherein the method consists essentially of applying the mixture to a cation-exchange or anion-exchange chromatography resin in a buffer, wherein if the resin is cation-exchange, the pH of the buffer is about 4-7, and wherein if the resin is anion-exchange, the pH of the buffer is about 6-9, and eluting the mixture at a gradient of about 0-1 M of an elution salt, wherein the monomer is separated from the dimers or multimers or both present in the mixture, and wherein the separated monomer has a purity of greater than 99.5% and the monomer yield is greater than 90%.